Combinatorial targeting of cancer bone metastasis using mRNA engineered stem cells.

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Public Summary:
BACKGROUND: Bone metastases are common and devastating to cancer patients. Existing treatments do not specifically target the disease sites and are therefore ineffective and systemically toxic. Here we present a new strategy to treat bone metastasis by targeting both the cancer cells ("the seed"), and their surrounding niche ("the soil"), using stem cells engineered to home to the bone metastatic niche and to maximise local delivery of multiple therapeutic factors. METHODS: We used mesenchymal stem cells engineered using mRNA to simultaneously express P-selectin glycoprotein ligand-1 (PSGL-1)/Sialyl-Lewis X (SLEX) (homing factors), and modified versions of cytosine deaminase (CD) and osteoprotegerin (OPG) (therapeutic factors) to target and treat breast cancer bone metastases in two mouse models, a xenograft intratibial model and a syngeneic model of spontaneous bone metastasis. FINDINGS: We first confirmed that MSC engineered using mRNA produced functional proteins (PSGL-1/SLEX, CD and OPG) using various in vitro assays. We then demonstrated that mRNA-engineered MSC exhibit enhanced homing to the bone metastatic niche likely through interactions between PSGL-1/SLEX and P-selectin expressed on tumour vasculature. In both the xenograft intratibial model and syngeneic model of spontaneous bone metastasis, engineered MSC can effectively kill tumour cells and preserve bone integrity. The engineered MSC also exhibited minimal toxicity in vivo, compared to its non-targeted chemotherapy counterpart (5-fluorouracil). INTERPRETATION: Our combinatorial targeting of both the cancer cells and the niche represents a simple, safe and effective way to treat metastatic bone diseases, otherwise difficult to manage with existing strategies. It can also be applied to other cell types (e.g., T cells) and cargos (e.g., genome editing components) to treat a broad range of cancer and other complex diseases. FUND: National Institutes of Health, National Cancer Institute of the National Institutes of Health, Department of Defense, California Institute of Regenerative Medicine, National Science Foundation, Baylx Inc., and Fondation ARC pour la recherche sur le cancer.

Scientific Abstract:
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